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Review

Mechanics and biology in intervertebral disc degeneration: a vicious circle

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SUMMARY

Intervertebral disc degeneration is a major cause of low back pain. Despite its long history and large socio-economical impact in western societies, the initiation and progress of disc degeneration is not well understood and a generic disease model is lacking. In literature, mechanics and biology have both been implicated as the predominant inductive cause; here we argue that they are interconnected and amplify each other. This view is supported by the growing awareness that cellular physiology is strongly affected by mechanical loading. We propose a vicious circle of mechanical overloading, catabolic cell response, and degeneration of the water-binding extracellular matrix. Rather than simplifying the disease, the model illustrates the complexity of disc degeneration, because all factors are interrelated. It may however solve some of the controversy in the field, because the vicious circle can be entered at any point, eventually leading to the same pathology. The proposed disease model explains the comparable efficacy of very different animal models of disc degeneration, but also helps to consider the consequences of therapeutic interventions, either at the cellular, material or mechanical level.

Introduction

Low back pain is a top-3 cause of disability in developed countries, and the number of people affected is increasing worldwide[1]. Up to 40% of adult persons in the United States report low back pain in the preceding 3 months, and with 20–33% of patients being unable to work, the disease has a major socio-economic impact[2,3]. In the Netherlands, recent policy changes in the management of low back pain have decreased expenditure, but the total costs are still 216 euro's per capita annually[3]. Prevention and therapeutic intervention is hampered because the veritable cause of low back pain remains unclear; however, a correlation with intervertebral disc degeneration has been documented[2,4–10]. Unfortunately, the aetiology of intervertebral disc degeneration is as obscure as the cause of low back pain, and the current consensus is that it is “multi-factorial”. Numerous changes in disc morphology and physiology have been described, but these alterations have not yet lead to a widely accepted disease model. The lack of an accepted explanatory model limits the understanding of this disabling disease, and hampers the development of effective therapies.

One of the issues to be resolved is the order and causal relationship of the biological and biomechanical alterations that occur in intervertebral disc degeneration. Some authors hypothesize that disc degeneration originates from biomechanical wear and tear[11–13]. Other authors focus on the disturbance of physiological cellular behaviour, mainly based on a loss of nutrition[14–17], but recently pathogens have been implicated as well[18]. However, these two viewpoints do not exclude each other, and it is conceivable that different pathological processes cause the same disease, equivalent to the etiological disease model of diabetes mellitus with subtypes 1 and 2. In fact, the dichotomy between biology and mechanics

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currently seen in the field may be unnecessary, as it has long been recognized that cellular physiology is affected by its mechanical environment[19,20]. This relationship, known as mechanobiology[21], has recently also been established for the intervertebral disc[22–24], and is deemed instrumental in developing intervertebral disc degeneration[25–29].

Similar to developing wrinkles in the skin, degeneration of the intervertebral disc is part of normal aging. In analogy to this, the painful degenerative disc disease[30] has been likened to accelerated aging of the disc[31]. As such, it is important to realize similar processes occur in aging and degeneration alike, and a clear discrimination between the two is difficult. Additionally, there is a strong genetic basis for intervertebral disc degeneration[32,33], because genetic information determines cellular behaviour and structural integrity of produced extracellular matrix. Therefore, polymorphisms in genes such as COLIA1 and or ADAMTS5 are a risk factor for developing degeneration at a younger age[34,35]. Nevertheless, neither age nor genetic make-up can be remedied; therefore, it is more relevant to look at what underlying processes are involved in order to halt or reverse intervertebral disc degeneration.

In this paper, we present a contemporary disease model of intervertebral disc degeneration. While this model can not explain low back pain, the development of a disease model is essential in identifying lapses in knowledge and development of therapies for associated intervertebral disc degeneration. Our disease model is based on the changes that occur in the nucleus pulposus, and is in the form of a positive feedback loop involving cells, extracellular matrix, and biomechanics (Fig. 1). Novel in this model are the mechanobiological cues that close the loop from biomechanics to cells, and involve a shift from hydrostatic stress to shear stress in the nucleus pulposus. In order to demonstrate that most common risk factors for developing intervertebral disc degeneration can initiate the positive feedback loop, we additionally apply the interactions in this model to human epidemiology, and observations in the different animal models for disc degeneration. The deliberation of the model will be preceded by a short introduction to the functional anatomy of the intervertebral disc and the changes of structures with degeneration.

The intervertebral disc and its anatomical structures in health and degeneration

Intervertebral discs are embedded between the vertebrae and provide flexibility to the spine. They consist of three anatomical parts: the nucleus pulposus, the annulus fibrosus, and the cartilaginous endplates. The nucleus is the core of the intervertebral disc, and is surrounded by the lamellae of the annulus fibrosus. Cranially and caudally the endplates limit the intervertebral disc, and form the anchoring into the vertebral bodies. Discus degeneration is associated with changes in all these anatomical structures.

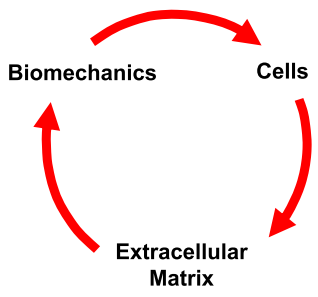

Fig. 1. Concept of the degenerative circle of intervertebral disc degeneration.

These alterations have been extensively reviewed in numerous papers[15,30,35–42], hence only short summary of the nucleus', annulus' and endplates' structure in a normal and a degenerated intervertebral disc will be provided.

A healthy nucleus pulposus is a gel-like, highly hydrated tissue, rich in proteoglycans[43]. The healthy nucleus pulposus generates an intradiscal pressure which separates the two vertebrae, tensions the annulus fibrosus, and distributes pressure evenly over the two adjacent endplates[41,44–46]. A degenerated nucleus pulposus is an unorganized fibrous tissue which has largely lost its capacity to bind water under compression[43]. Therefore, the pressure in the nucleus pulposus is dwindling[47], and disc height is lost[45,46]. Overall, the nucleus undergoes the highest degree of remodelling during intervertebral disc degeneration[44,48].

A healthy annulus fibrosus is a highly organized fibrous structure. It consists of ~20 concentric lamellae of alternating oblique collagen fibres interspersed with proteoglycans[49,50]. The collagen fibres are tensioned by intradiscal pressure through two mechanisms: direct radial pressure from the nucleus pulposus, and cranial-caudal stretch from the separation of the two endplates[41,44,45]. Due to a loss of intradiscal pressure, the annulus fibrosus of a degenerated intervertebral disc deforms by in- and out-ward bulging and buckling[45,51,52], and shows progressive increase of structural defects such as: rim lesions, de-lamination and radial fissures[30,41,49]. Remarkably, despite these structural changes, there is hardly any loss of tensile strength[53,54]; however, hydraulic permeability changes from anisotropy favouring the radial direction to isotropy[55,56], which could affect the build-up of intradiscal pressure.

Healthy vertebral endplates are of uniform thickness, do not bulge into the vertebrae and appear as homogeneous hyaline cartilage[51,57]. With intervertebral disc degeneration, there is an increase in microscopic and macroscopic damage to the endplate[37,58]. Additionally, there is a marked increase in sclerosis of the subchondral bone[59–61], similar to degenerated cartilage[62]. Changes in endplate and subchondral bone morphology (e.g., fractures or endplate sclerosis) have also been implicated as preceding intervertebral disc generation (by decompression of the nucleus[12,31,63,64] or impairment of nutrition[16,60,65], respectively). Overall, the endplate can be deemed an important part of the intervertebral disc, because damage to the endplate is strongly related to both intervertebral disc degeneration and low back pain[5,58,66,67].

Overall, a degenerated intervertebral disc differs from a non-degenerated intervertebral disc in that there is a marked loss of disc height, a fibrous dehydrated nucleus, in- ward and out-ward buckling of annulus fibres, extensive endplate damage, and sclerosis of the subchondral bone.

Degeneration of the intervertebral disc; an interaction between cells, extracellular matrix, and biomechanics

The nucleus pulposus radiographically shows the most extensive changes in intervertebral disc degeneration[44,48,68], and it is therefore the most thoroughly investigated. Both the annulus fibrosus and cartilaginous endplates have received attention in their relationship with intervertebral disc degeneration; however, changes in these structures are less well documented[37,51]. Therefore, this section will focus on the changes in the nucleus pulposus, followed by a short summary of the effect of nucleus degeneration on the annulus and endplates, and vice versa. We will discuss the cells in the nucleus pulposus and their interaction with the surrounding matrix; the effect of the shift of matrix composition on the biomechanical behaviour; and the subsequent effect of biomechanical stresses on cellular physiology. This will show the progressive nature of intervertebral disc degeneration to be a

positive feedback loop as shown in it's basic conceptual form (Fig. 1).

Cells: from notochordal cells to nuclear chondrocytes

In the human nucleus pulposus, notochordal cells that are present from the early embryonic formation of the intervertebral disc[69,70] show a gradual transition towards chondrocyte-like cells in the first decade of life[37,38]. Recently murine fate mapping studies demonstrated that the mature chondrocyte-like cells in the nucleus pulposus cells are derived from the embryonic notochord[71,72]. These mature nuclear chondrocytes produce collagen type I, but reduced amounts of water-attracting proteoglycans and collagen type II[42]. Thus, the transition of the cell population in the nucleus pulposus from predominantly notochordal cells to chondrocyte-like cells leads to a decrease in proteoglycan synthesis and therefore affects the potential of the nucleus pulposus to maintain it's structure and composition[73,74].

Cells – extracellular matrix: from anabolism to catabolism

In the degenerating intervertebral disc, there is a progressive increase in the expression of inflammatory cytokines like IL-1 and TNFα[75–77]. These cytokines, expressed by nucleus cells, up-regulate matrix remodelling involved in intervertebral disc degeneration[75,78]. Matrix remodelling by the nucleus cells is mainly mediated by two families of enzymes: Matrix Metallo Proteinases (MMP) and A Disintegrin And Metalloproteinases with Thrombospondin Motifs proteins (ADAM-TS)[36,79]. Some non-proteolytic degradation is also present due to glycation[80]. In later stages of disc degeneration, inflammatory cytokines also enhance neurovascular in-growth and pain response[75,78]. Altogether, there is a progressive reduction in the expression of proteoglycans and collagen type II genes with increasing degeneration[36,42,48,81]. Simultaneously, collagen type I expression is increased, which indicates a change in matrix stresses[82].

Extracellular matrix: from proteoglycans to collagen type I

The nucleus pulposus extracellular matrix consists of proteoglycans and collagens, and aggrecan is by far the most abundant proteoglycan in the nucleus[43]. Proteoglycans have a negative charge, which causes an osmotic pressure of 420–450 mOsm[83]. This osmotic pressure attracts and binds water to the extracellular matrix. In degeneration, aggrecan is cleaved from the hyaluronic acid backbone[84,85]. Cleaved aggrecan fractions do not aggregate[43], making them less effective in binding water. Furthermore, there is a shift of predominantly collagen type II to collagen type I in the nucleus[42]. Overall, the biochemical content of the extracellular matrix changes from predominantly proteoglycans and collagen type II to a more fibrous tissue consisting primarily of collagen type I, resulting in a loss of water-binding potential.

Extracellular matrix – biomechanics: a reduction in intradiscal pressure

In healthy discs, the negative charge of the proteoglycans generates an osmotic potential, which is translated into a biomechanical hydrostatic pressure through the attraction of water. This intradiscal pressure is approximately 0.1–0.24 MPa when lying supine, and increases linearly with loading of the disc[47,86–88], up to more than 2.0 MPa[86]. The quantity of bound water can vary, which changes the intrinsic intradiscal pressure[89]. In healthy discs, this decrease or increase of bound water is due to poro-elastic fluid flow upon loading or unloading of the disc, respectively[46,90]. In degenerating discs, the increased fragmentation of aggrecan reduces its effective negative charge, which decreases intradiscal pressure[47] and the ability to retain water under compressive forces[91], which is reflected in the reduction of disc height[44,46]. The effect of a reduction of collagen type II and an increase of collagen type I on the biomechanical function of the nucleus matrix is unknown. However, as collagen type II is more compliant than collagen type I, an increase of nuclear shear stresses is expected.

Biomechanics: from hydrostatic pressure to shear stress

Intradiscal pressure is essential for the maintenance of biomechanical behaviour of the intervertebral disc. Intradiscal pressure tensions annulus fibres, and supports the endplate, and as such is the main determinant of disc height and stiffness in axial compression[45,46]. In degenerated intervertebral discs, disc height and axial compliance are reduced, and radial bulge is increased[45,46,92]. Another effect of the reduced intradiscal pressure in the intervertebral disc is the disturbed stress distribution found in degenerated discs[30,93]. This disturbance in stress distribution generates stress concentrations, which increases the risk of endplate fractures or Schmorl's nodes, which are increasingly seen with disc degeneration[66].

A reduction in intradiscal pressure leads to increased shear stresses in both the nucleus pulposus and the annulus fibrosus upon axial compression of the spine[17,90]. Due to loss of tension in the annulus fibrosus, motion segments with reduced intradiscal pressure also have an enlarged neutral zone in shear, bending, and torsion[41,45,94–98]. The resultant changes in bending and torsion behaviour of the motion segment may further increase shear stresses in the nucleus and remodelling of the extracellular matrix. Thus, the reduction of intradiscal pressure reduces disc height; increases stress concentrations within the disc; and increases shear forces in the nucleus.

Biomechanics – cells: a change in matrix stresses alters cellular physiology

The concept that the mechanical environment of cells is important for cell function is not new. In 1862, Hueter and Volkmann independently hypothesized that mechanical stimuli directly influence cellular function and matrix synthesis in bone and joints due to local differences in tension and pressure[19,20]. Today, the effect of biomechanical forces on cellular function is known as mechanobiology[11,21,25,28]. Several research groups have shown that a distinct compressive force on the spinal motion segment, both *in vivo* and *ex vivo*, can cause catabolic, anabolic and inflammatory cell responses in the intervertebral disc[23,26,99–102]. Also the temporal characteristics of loading are important as cyclic loading has been shown to be beneficial as opposed to static loading[22,99,103,104]. As a result, the relationship between mechanical behaviour and cell function is argued to be a pivotal component of intervertebral disc function and dysfunction[25,27,28,105].

Cells throughout the intervertebral disc respond to changes in hydrostatic pressure. In the nucleus, the proteoglycan production at 0.3 MPa is roughly 20% higher than at 0.1 MPa[106,107]. Additionally, MMP-3 production is reduced, and tissue inhibitor of metallo proteins-1 (TIMP) production is increased[106,107], which reduces remodelling of the extracellular matrix. This pressure sensing mechanism of nucleus cells appears to be impaired in cells from degenerated discs as they respond less anabolic to physiologic intradiscal pressure[108]. Cells also respond to the osmotic pressure of the extracellular matrix, with an optimum proteoglycan production at pressures between 400 and 500 mOsm, and a reduced synthesis of aggrecan with declining or increasing osmotic

pressure[83,109–111]. A decline in osmotic pressure increases MMP-3 production[111], and precludes hypertrophy of the normally hyperosmotic nuclear chondrocytes[17,112]. Thus, in degenerating intervertebral discs, the drop in intradiscal and osmotic pressure will reduce the anabolic stimulus and increase catabolic stimuli to the nuclear chondrocytes.

The shift of hydrostatic pressure to shear stresses in the intervertebral disc has a distinct mechanobiological effect on the nuclear chondrocytes[90,113,114]. Similar to other load-bearing tissues like cartilage and bone, the increase in shear stress will initiate the formation of a fibrous tissue, rich in collagen type I[25,82,114,115]. Furthermore, increased shear stress increases the production of nitric oxide by chondrocytes[114]. Nitric oxide is a reactive oxygen metabolite that reduces proteoglycan production, and increases apoptosis in cartilage and in the intervertebral disc[114,116,117]. Thus, reduction of intradiscal pressure increases shear stresses in the nucleus, and both may accelerate degeneration in the intervertebral disc.

Nucleus homeostasis depends on endplate and annulus integrity

Although we have focussed on the nucleus pulposus in this section, the homeostasis of the nucleus is dependent on the confines of a functional annulus and intact endplates[109,118]. If damage to either of these structures occurs, the nucleus is decompressed[12,119], and exposed to inflammatory cells from outside the disc[78]. Both these effects will result in the degenerative cascade described above. Conversely, if the nucleus is degenerated, this will also affect the annulus and the endplates. In the annulus, the reduction of intradiscal pressure will reduce tension in annulus fibres[45] and increase in- and out-ward bulging[12,52]. This bulging can increase shear forces between laminae[120], leading to delamination of the translamellar bridges[121], and consecutive risk of tears[52]. In the endplates, the loss of annulus tension and the reduced stress distribution by the nucleus will alter the biomechanical stresses on the endplates[12,44], which may be the cause of endplate sclerosis, fractures, or Schmorl's nodes[66].

In summary, the interaction of cells, extracellular matrix and biomechanical stress is instrumental in homeostasis of the intervertebral disc. In intervertebral disc degeneration this balance is disturbed. If the cells do not receive the proper mechanical and chemical cues they will stop producing, or even start degrading proteoglycans. A reduction in proteoglycans will lead to a drop of the intradiscal pressure, which will alter the biomechanical stresses on the cells. From this, one can deduce a positive feedback loop of intervertebral disc degeneration, which contains cells, extracellular matrix, and biomechanics: the degenerative circle (Fig. 2).

Application of the degenerative circle

The degenerative circle illustrates the progressive nature of intervertebral disc degeneration, but can also explain the different aetiologies of intervertebral disc degeneration. In this section, we investigate the application of the degenerative circle in understanding human epidemiology and animal models for intervertebral disc degeneration. In human epidemiology, aberrant biomechanics (e.g., frequent lifting[122]); chemical stress to cells (e.g., smoking[123]); or damage to the extracellular matrix (e.g., discography[124]); all lead to intervertebral disc degeneration. Additionally, induction of intervertebral disc degeneration in animal models can be effectuated through: altered disc biomechanics, changes to cell physiology, and damage to the nucleus, annulus, or endplates. This section will provide examples of the initiation of degeneration through each of the three domains, i.e., biomechanics, cells, and extracellular matrix. By applying the model from different angles, we aim to infer the generic nature of the degenerative circle, as all discussed examples of human epidemiological occurrence of disc degeneration and animal models apparently lead to a similar degeneration of the intervertebral disc (Fig. 3). To illustrate the independence of starting at a specific point in the circle, we start this section by discussing biomechanics.

Biomechanics: induction of degeneration

In literature the biomechanical “wear and tear” has long been thought to be a major cause of intervertebral disc degeneration[32,125], mainly because low back pain and degeneration occur, more frequently than in the general population, in manual labour

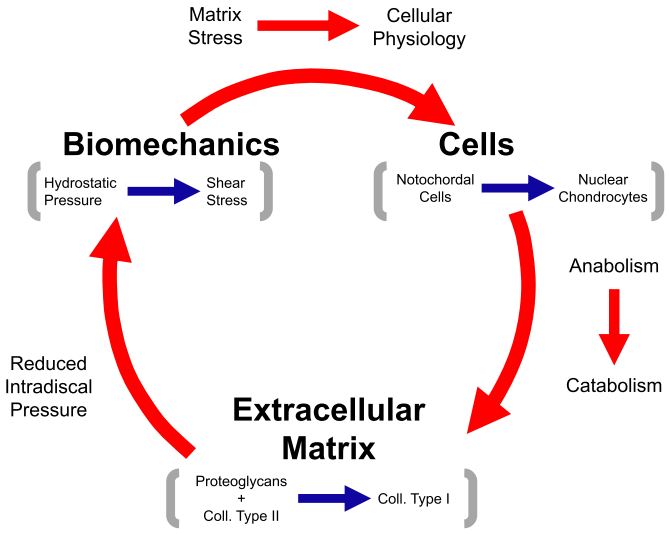

Fig. 2. The degenerative circle of intervertebral disc degeneration. Homeostasis of the intervertebral disc is dependent on the interaction of cells, extracellular matrix and biomechanical stress. If this balance is disturbed, the cells stop producing proteoglycans, this will give a reduction in hydrostatic pressure and increase shear forces on the cells. An increase of shear forces further decreases the production of proteoglycans, leading to progressive degeneration.

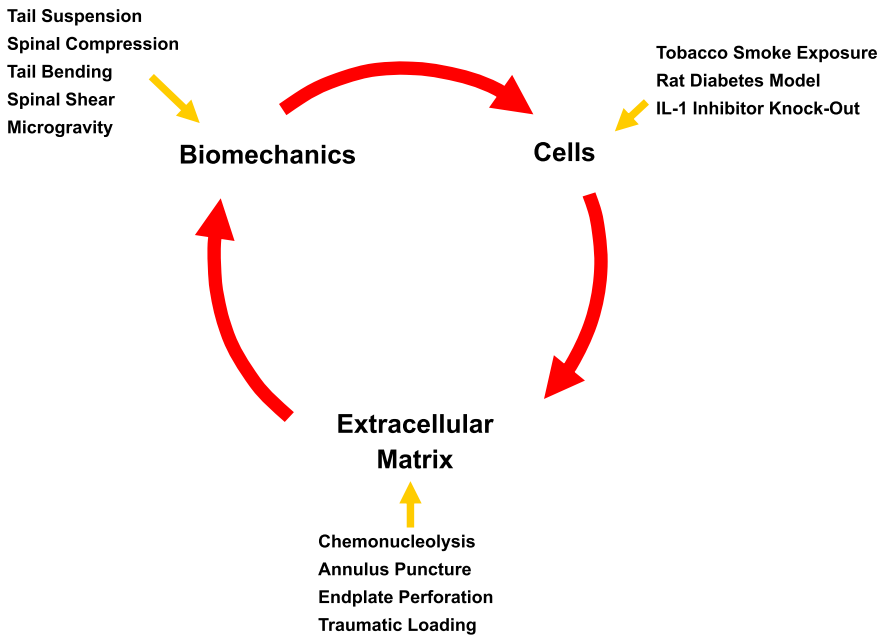

Fig. 3. The efficacy of animal models applied to the degenerative circle. Intervertebral disc degeneration can be induced through any of the three main elements of the degenerative circle, which further indicates a positive feedback loop.

workers[7], machine drivers[7], soldiers carrying loads[126], but also in elite athletes[127–129]. Interestingly, all astronauts experience low back pain upon the exposure to microgravity, and on their re-entry[130,131], which both may be caused by over-pressurization of the nucleus. Although genetic research has nuanced the role of biomechanical factors in intervertebral disc degeneration[32], there still is a link between high loading on the low back and both intervertebral disc degeneration and low back pain[5,7,58,132–134].

An abundance of animal models uses altered biomechanics to induce intervertebral disc degeneration, including: Tail suspension/Hind leg unloading[135,136]; Tail or spinal compression[26,137–140]; tail bending[141–143]; spinal shear stress[113], and microgravity[144,145]. These models show that although the intervertebral disc is left intact, the altered biomechanical load leads to a catabolic cell reaction and remodelling of the intervertebral disc matrix over time. Apparently, in animal models, it does not matter whether the disc is overloaded, unloaded or aberrantly loaded: altering the biomechanical environment of the intervertebral disc induces a catabolic cell reaction with detrimental effects on the extracellular matrix.

Cells: induction of degeneration

One of the most influential paradigms on intervertebral disc degeneration is that a reduction in nutrition of disc cells leads to a catabolic shift[15,16,35,65]. The hypothesis is that this is due to the sclerosis of the endplates, which limits endplate pores and subsequent vascular supply[60]. It has been established that diffusion into the disc changes with progression of intervertebral disc degeneration[146]. However, the origin of endplate sclerosis should be further elucidated to determine whether endplate sclerosis is in fact the cause, or merely an effect of degeneration due to altered biomechanical stresses in the endplates. Other risk factors like smoking[32,123] and diabetes mellitus[147], most likely induce disc degeneration by their effect on cellular physiology. Interestingly, these risk factors may also affect the nutrition of the nuclear chondrocytes by their detrimental effects on microcirculation[35,148–151]. Additional to the effects of nutrition, low-grade infection could possibly trigger the cells to degrade the matrix of the intervertebral disc[18,152], similar to arthritic diseases[153–155].

Intervertebral disc degeneration is found in mice which are exposed to tobacco smoke[156,157], and in rat models for diabetes[158,159]. The exact pathophysiological pathway is not clear, but some information may be gleaned from these experimental models. Disc degeneration in tobacco smoke models is not mediated by genotoxic DNA damage, but by an alteration of cell physiology[160]. This may be caused by the increase of the nitric oxide concentration in the blood, which reduces proteoglycan synthesis[116]. In diabetes models, hyperglycaemia could play a role, either by a direct effect on nucleus cells[161,162], glycation reactions with aggrecan[80], or by the increase of the osmotic value of the blood. However, in both models a biomechanical effect cannot be excluded. In smoke models, the vertebral bodies show a marked increase in porosity, which reduces the structural integrity. In diabetes models, the overweight may induce overloading. Again, it could also be the negative effect on the microcirculation that both smoking and diabetes mellitus have in humans; however, to our knowledge, the effect of smoking or diabetes on endplate microcirculation has not yet been investigated in animal models.

Evidence for induction of intervertebral disc degeneration through a catabolic shift in cells is not well established in animal models, but there is evidence from IL-1-inhibitor knock-out mice (IL-1rn$^{-/-}$) that raised levels of IL-1β coincide with intervertebral disc degeneration after 55 days[163]. *Ex vivo*, injection of MMP-3, ADAM-TS4 or HTRA-1 showed little effect on catabolic gene expression after 8 days[164]; however, TNFα addition to the culture medium has been shown to have a persistent catabolic effect on disc cells up to 21 days[76]. Infectious processes that induce intervertebral disc degeneration have to our knowledge not been investigated in animal models.

Extracellular matrix: induction of degeneration

Herniation of the nucleus[165], puncture of the annulus[124], or endplate fracture[63,166] are associated with the long-term risk of disc degeneration in humans. This damage can be induced through a

single traumatic overload[166,167], which can damage the extracellular matrix, both macroscopically[12,165] and microscopically[168]. This results in a loss of intradiscal pressure[119,166,169], and significantly elevated levels of interleukin (IL)-5, IL-6, IL-7, IL-8, MCP-2, GROα, MIG and NGF[166,167]. Interestingly, it appears that the damage to the matrix, either endplate or annulus, is essential for developing intervertebral disc degeneration, rather than simply the absorption of a distinct amount of energy[170]. The induction of degeneration then occurs by decompression of the nucleus[119,166,169], exposure of nucleus cells to matrix fragments[171], response to neurotrophic and angiotrophic factors[78], or a combination thereof. This illustrates that within the domain of extracellular matrix there are different pathways into the degenerative circle[31], which appear to depend upon decompression and exposure of the nucleus[12,166].

In animal models, damage to the extracellular matrix is the most commonly used method of induction of intervertebral disc degeneration. Whether the damage is done by chemonucleolysis[172–175], annulus puncture[176–179] or endplate perforation[169,180], progressive degenerative disc degeneration is seen. Unfortunately, a comparison of the chronological order of cellular and biomechanical changes between these different methods of degeneration induction has not been performed. However, it has been established that pressure drop[181] and the expression of catabolic agents[170,182,183] occur both *ex vivo* and *in vivo*. Interestingly, it has been shown that disc stress distributions in the IVD are influenced more by damage to the endplate than by injuries to the outer annulus[64], but again, direct comparison of the differences in cellular changes between these two pathways has not yet been performed.

In summary, both in human epidemiology and in animal models there is evidence for numerous pathways towards progressive disc degeneration. This is important because it illustrates why intervertebral disc degeneration has been called multi-factorial. The degenerative circle can explain most of the common risk factors for intervertebral disc disease, and the progressive nature of degenerative disc disease.

Discussion

In this paper we propose a model for intervertebral disc degeneration: the degenerative circle. This model is based on the most prominent alterations that occur in the nucleus pulposus in intervertebral disc disease, and consists of a positive feedback loop involving cells, extracellular matrix, and biomechanics. Additionally, this paper aims to provide insights into the pathways into the degenerative circle based on human epidemiology and animal models for intervertebral disc degeneration.

Both Adams *et al.*[11] and Colombini *et al.*[184] have proposed pathophysiological models for intervertebral disc degeneration that include some of the relations of the degenerative circle. The model of Adams *et al.* focuses on structural damage to the extracellular matrix and is progressive due to a frustrated cellular healing response, mainly because of a drop of intradiscal pressure. Their model thus differs in two fundamental ways: firstly, it only allows for disc degeneration to occur upon damage to the extracellular matrix. Secondly, in their model, mechanobiological cues are limited to a decrease in intradiscal pressure, and do not include an increase in shear stresses. However, this seems crucial for the breakdown of aggrecan, and the transdifferentiation to collagen type 1 producing cells. The model of Colombini *et al.* regards chronic abnormal load as the main cause of intervertebral disc degeneration; they state that this will lead to a catabolic cell response, and consecutively an altered matrix. There are similarities with the degenerative circle; however, again their model differs in crucial ways: their model does not allow for aberrant cell physiology or damage to the extracellular matrix to induce disc degeneration, nor does it elaborate on how the catabolic cell response is induced. Furthermore, their model does not stress the progressive nature through a positive feedback loop. The degenerative circle thus presents a more complete view of intervertebral disc degeneration as it allows for multiple ways of induction of intervertebral disc degeneration, illustrates the progressive nature through a positive feedback loop, and is the first to elaborate on the mechanobiological cues that play a role in intervertebral disc degeneration.

The degenerative circle is a simple model. It provides a practical tool for clarifying the complex interactions of intervertebral disc disease to patients, medical students, and clinicians. Additionally, this model stresses the importance of the interaction between cells, extracellular matrix and biomechanical behaviour, and illustrates that all are important in intervertebral disc degeneration. This is essential because all three domains and their interactions need to be considered if we want to reverse or halt the degenerative process. However, the simple elegance of the degenerative circle has intrinsic shortcomings as it contains some oversimplifications.

Weaknesses in the proposed model include a lack of other feedback mechanisms in intervertebral disc physiology. Clearly, besides a pathway through biomechanical changes, there is an also a direct feedback loop from the extracellular matrix to the cells. This is mainly dominated by the osmotic charge of the proteoglycans. Numerous other mechanisms (e.g., endplate sclerosis[65], the effect of loading on nutrition[185], low-grade infection[18], toll-like receptor stimulation[171,186]) could later be added to the model, when their effects are further quantified. It is interesting to note that feedback mechanisms in intervertebral disc degeneration seem to progress the disease rather than halt it, which is remarkable since feedback loops usually poise homeostasis in human physiology. Therefore, more research could be performed to indentify anabolic feedback mechanisms in the intervertebral disc. Due to these and other possible effects, the degenerative circle should not be regarded as a definitive model for intervertebral disc degeneration, but rather as the backbone of a more detailed model.

The choice of excluding genetic influences in the degenerative circle was made to simplify the current disease model; however, from the literature it is known that genetic influences play a substantial role in developing intervertebral disc degeneration[32,33]. A loss of matrix integrity due to genetic defects (e.g., Col I, Col IX, VitD, Aggrecan, MMP-3 and MMP-9), has been shown to play a role in the

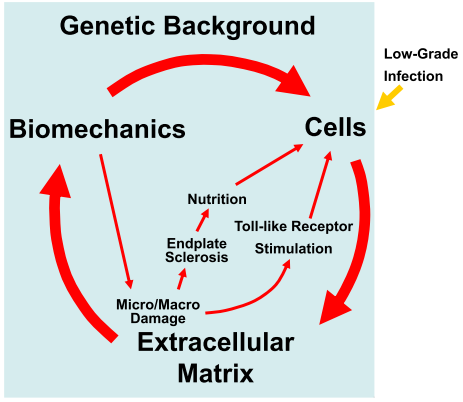

Fig. 4. Additions to the degenerative circle. The degenerative circle is not a final account of intervertebral disc degeneration, possible future additions to the model are included. It is also important to notice that the degenerative circle is drawn upon an individual's genetic background, which probably influences all pathways included in the model.

development of intervertebral disc degeneration[35,187]. Moreover, Rajasekaran *et al.* recently showed that the development of either endplate damage, disc height loss or annulus tears was associated with deficits in specific genes which code for the extracellular matrix of respective intervertebral disc parts[34]. Additionally, there is a clear role for genes in the biomechanical forces (e.g., length, weight[188]), and probably also for the mechanobiological response to biomechanical forces[108]. Therefore, the genetic make-up of single patients can be viewed as the background upon which the degenerative circle is drawn, this is shown in Fig. 4, along with the possible additions to the model.

Animal models studied in a longitudinal manner can be useful in unravelling different cascades of disc degeneration, and understanding the timing of changes. Further understanding of the timing of degenerative changes is essential in the development of prevention and therapies for intervertebral disc degeneration. Chondrodystrophic and non-chondrodystrophic dogs provide an interesting study population as the former develops early disc degeneration whereas the latter only develops disc degeneration at advanced age[189]. This could help distinguishing between aging and degeneration, but also indicate what changes precede, and what changes follow. Furthermore, comparison of the timing of changes between different ways of inducing disc degeneration (e.g., chemonucleolysis vs smoking induced degeneration, or diabetes models vs overloading) may shed a light on whether genetics, environment, or matrix damage indeed provide a similar disc degeneration, or whether if there are differences (and the current disease model should be updated).

The degenerative circle is a model for the multifaceted disc degeneration, but does not explain why some people get low back pain and others do not. It is important to consider that low back pain is a very heterogeneous symptom, in which a discogenic origin is just one of the causes[190]. Discogenic back pain in itself is probably also heterogeneous, depending on damage to innervated parts of the intervertebral disc (i.e., endplate or annulus)[31]. Additionally, the nucleus could also give rise to discogenic back pain, especially upon in-growth of nerve fibres[75,191]. These could be triggered by the increase in inflammatory cytokines[75–77], which are increasingly produced with degeneration of the hyaluronic acid backbone[171]. This in-growth of nerve fibres should especially be considered in end-stage disc degeneration when intradiscal pressure drops below blood pressure[47], and the relationship with low back pain is clearest[10]. Astronauts provide an interesting source for investigating discogenic low back pain, they are healthy but immediately upon spaceflight and re-entry experience debilitating low back pain[130,131]. Hypothetically, this could be due to straining of the annulus upon unloading in space, and overloading of the endplates upon re-entry. Their high tendency of developing nucleus protrusion upon re-entry at least indicates a very high intradiscal pressure[131,192], which has been indicated as a source of discogenic pain[190]. Degeneration of the intervertebral disc could also strain the facet joints due to disc height loss[193]. Similarly, a reduction of intradiscal pressure increases the neutral zone[95,97,98], which transfers the stabilization of the segment from the disc to adjoining ligaments and muscles[194]. Finally, it is important to consider that the speed of progression through the degenerative circle may depend on the original damage, and pain could be related to the speed of progression[31].

The use of the degenerative circle as a model for intervertebral disc degeneration has several implications for therapeutic intervention. Currently, there is no cure for intervertebral disc disease; it cannot be reversed, and there is no evidence that it can be slowed down. The degenerative circle provides insight into the disease because it shows that all domains of intervertebral disc degeneration are interdependent (Fig. 2). As such, it suggests that therapies may be more successful if they affect multiple domains of the degenerative circle in order to slow down or reverse the progressive structural failure (a reversal of the arrows in Fig. 2). An example of such a multi-disciplinary intervention would be a cell-loaded, osmotically active nucleus replacement accompanied by patient-specific physiotherapy. That there is intrinsic healing potential becomes more and more clear, as progenitor cell activity remains present in the human nucleus pulposus[74,195,196]. Furthermore, healing potential in the bovine caudal disc has been shown by the application of physiological loads after chemonucleolysis *ex vivo*[24]: after 14 days, proteoglycan content was restored to pre-intervention levels. However, as this was a model of early disc degeneration, the question arises: is there a point of no return? Additionally, as intervertebral disc degeneration usually develops over years, the duration of such therapies should be considered. Extensive coverage of implications for therapy falls outside the scope of this paper, but this example shows the multi-disciplinary challenge that researchers face when tackling intervertebral disc degeneration.

Intervertebral disc degeneration and the degeneration of joint cartilage as seen in osteoarthritis show marked similarities, although they are rarely discussed simultaneously. Striking similarities are seen on plain radiographs: the loss of disc height or joint space; the sclerosis of the subchondral bone; and the development of osteophytes. Furthermore, the extracellular matrix is comprised of similar constituents (but in another ratio), and similar matrix-degrading enzymes are present in the process of degeneration. There are also differences such as the type of forces applied to the matrix, and the absence of synovial fluid in intervertebral discs; however, a similar degenerative circle could be a model for osteoarthritis.

Conclusion

The degenerative circle provides a comprehensive model for a contemporary view on intervertebral disc degeneration. It includes a catabolic cell response, changed extracellular matrix, and altered biomechanics. Rather than just simplifying the disease, it also illustrates the complexity as all factors are interdependent, which is why intervertebral disc degeneration has often been called multifactorial. It solves some of the controversy surrounding biomechanics, wear and tear, and cellular physiology by pointing out their interdependency and that all can initiate the degenerative process. Thereby, the model explains some of the human epidemiology and the efficacy of animal models. Because all factors are interrelated, it illustrates why intervertebral disc degeneration is hard to halt or reverse. Rather than being the definitive model for intervertebral disc degeneration, the degenerative circle can serve as a backbone to improve scientific discussion and speed-up therapeutic advancement.

Author contributions

PV: Conception and design, Collection and assembly of data, Analysis and interpretation of the data, Drafting of the article, Final approval.

IK: Conception and design, Analysis and interpretation of the data, Drafting of the article, Final approval.

KE: Conception and design, Critical revision of the article for important intellectual content, Final approval.

RH: Conception and design, Critical revision of the article for important intellectual content, Final approval.

TW: Conception and design, Critical revision of the article for important intellectual content, Final approval.

BR: Conception and design, Critical revision of the article for important intellectual content, Obtaining of funding, Final approval.

JD: Conception and design, Analysis and interpretation of the data, Critical revision of the article for important intellectual content, Final approval.

TH: Conception and design, Analysis and interpretation of the data, Critical revision of the article for important intellectual content, Obtaining of funding, Final approval.

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Conflict of interest

None of the authors have any conflict of interest to declare.

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